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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/716,209	10/09/1996	LAURENT PRADIER	ST94014-US	5539

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WILEY, REIN & FIELDING, LLP
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EXAMINER
GUCKER, STEPHEN

ART UNIT	PAPER NUMBER
1647	41

DATE MAILED: 04/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Acti n Summary

Application No.	Applicant(s)
08/716,209	Prudier et al.
Examiner	**Group Art Unit**
Stephen Gucker	1647

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☑ Responsive to communication(s) filed on 1/28/03.

☑ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☑ Claim(s) 27-28, 31-35, 37-38, 40-54 is/are pending in the application.

Of the above claim(s) 42-47 & 51-54 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☑ Claim(s) 27-28, 31-35, 37-38, 40-41 & 48-50 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☑ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☑ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been ☑ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Reference(s) Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Other _____

Office Action Summary

Response to Amendment

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. Any objections or rejections made in a previous Office Action that are not herein reinstated have been withdrawn.

3. The disclosure is objected to because of the following informalities: The first sentence of the specification claims the benefit under 35 USC 120 and 365(c) of co-pending US Application Serial No. 08/403,868. However, the first sentence of the specification fails to identify if the instant Application is a continuation, divisional, or a continuation-in-part of 08/403,868. The instant application is being treated as a continuation-in-part of 08/403,868 since Applicant has made a statement of record that "there are clear differences between the specification of this application and the WO/94/08026 document" and "one of skill in the art would have no difficulty identifying the differences between the specification of this application and the published WO 94/08026 document" (Paper No. 36, filed 5/23/02, pages 4-5). The WO 94/08026 document is also known as PCT/EP93/02519, and 08/403,868 was a U.S. National Phase filing of PCT/EP93/02519, so the specification of 08/403,868 must be identical to that of PCT/EP93/02519, otherwise known as WO 94/08026.

Appropriate correction is required to claim the benefit of 08/403,868.

4. Applicant is required to update the continuing data of the first sentence of the specification to indicate that 08/403,868 is now abandoned and no longer co-pending.

5. Claims 27-28, 31-35, 37-38, 40-41, and 48-50 are rejected under 35 U.S.C. § 102(f) because the applicants did not invent the claimed subject matter. The claimed products encompassing a replication defective recombinant adenovirus comprising a cDNA encoding brain-derived neurotrophic factor (BDNF) are disclosed in foreign priority document EP92-402644.6, filed September 25, 1992. It is noted that this same foreign priority document is the priority document in WO 94/08026, which is the published international application also known as PCT/EP93/02519 which was recited in the first sentence of the specification and the inventorship of WO 94/08026 is Axel Kahn, Jacques Mallet, Michel Perricaudet, Marc Peschanski, Jean-Jacques Robert, and Le Gal La Salle which differs from the instant inventive entity. The claimed invention is set forth in the foreign priority document and WO 94/08026, but the inventorship of WO 94/08026 is different from the instant Application even though both the instant Application and WO 94/08026 claim benefit of the same foreign priority document. Because of this ambiguity concerning the inventorship of the foreign priority document, it is incumbent on applicants to provide a satisfactory showing which would lead to a reasonable conclusion that applicants alone are the inventors of the claimed invention. To resolve the ambiguity, applicants may file declarations by the non-applicant co-authors of the references disclaiming the invention or a declaration by applicants setting forth the facts which provide an explanation as to why the non-applicants Axel Kahn, Jacques Mallet, Marc Peschanski, Jean-Jacques Robert, and Le Gal La Salle are not inventors. Applicant is reminded of the requirement for identity of inventorship between a U.S. application and a 35 U.S.C. 119 priority application.

See MPEP § 201.13 and 2137.01.

Applicant's arguments filed 5/23/02 have been fully considered but they are not persuasive because Applicant argues that "Joint inventors A and B in a nonprovisional application filed in the United States Patent and Trademark Office may properly claim the benefit of an application filed in a foreign country by A and another application filed in a foreign country by B, i.e., A and B may each claim the benefit of their foreign filed applications. M.P.E.P. §201.13." (Paper No. 36, filed 5/23/02, page 4). Because there are not separate inventors of the instant inventive entity claiming foreign priority to separate foreign priority documents in the instant Application, this argument is unconvincing and unpersuasive because it is not on point, i.e. in the instant Application, all inventors are claiming foreign priority in common to two different foreign priority documents, not some inventors claiming priority to one document and other inventors claiming priority to a different document. Applicant is again reminded of the requirement for identity of inventorship between a U.S. application and a 35 U.S.C. 119 priority application. See MPEP § 201.13 and 2137.01. The case law cited by Applicant is not relevant to the instant Application because it does not deal with foreign priority. Furthermore, the case law concerns a component of a claimed invention designed by a vendor or a product modified to meet a particular requirement. That is clearly and unambiguously not the fact pattern of the instant Application where almost the entire invention is disclosed in 08/403,868 and WO 94/08026.

In addition, left unexplained by Applicant is the relationship of Axel Kahn, Jacques

Mallet, Marc Peschanski, Jean-Jacques Robert, and Le Gal La Salle to the instant Application when all are named as inventors of both 08/403,868 and WO 94/08026 which the instant Application claims the benefit of, but who are not listed as inventors of the instant Application.

As to Applicant's argument that WO 94/08026 is not drawn to the invention presently disclosed in the instant Application, the Examiner respectfully disagrees. WO 94/08026 teaches replication defective adenoviruses of type 2 or 5 (Ad2 or Ad5) which are devoid of either one or both of their E1 and E3 regions, contain the MLP, E1a, CMV, RSV-LTR , or neural or glial promoters, can encapsulate, and encode BDNF (pages 3, line 28 to page 4, line 31 and page 6, line 25 to page 7, line 3). In addition, WO 94/08026 specifically and explicitly teaches the Ad.RSVb-gal adenovirus (page 10, line 11) which, contrary to Applicant's assertion that WO 94/08026 does not teach the "additional structures of the adenovirus vectors discussed" in the instant Application, does, in fact, teach these additional structures as shown by the Reply to Request for Information, Paper No. 40, filed 1/28/03, pages 2-3.

6. All of the instant claims recite or depend from claims which recite the limitation of an adenovirus E1 gene which is non-functional. However, neither foreign priority document EP92-402644.6, filed September 25, 1992, or WO 94/08026, which is the published international application also known as PCT/EP93/02519, filed September 17, 1993, disclose an E1 gene which is non-functional. The aforementioned priority documents describe an adenovirus where the E1 gene is merely lacking or deleted, which is distinguished from non-functional in the instant Application (see pages 9-10 of the instant specification). Therefore, in addition to the

102(f) rejection set forth above, none of the instant claims receive the benefit of any effective filing priority before 3/18/94, the filing date of foreign priority paper FR94/03191, which foreign priority now has been perfected because a translation has been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

7. The Examiner is making a request for information under 37 CFR 1.105. A critical issue in determining what prior art reads on the instant invention concerns the definition of a "deleted" as opposed to a "non-functional" E1 gene (see pages 9-10 of the instant specification). Most of the information provided in the Reply to Request for Information (Paper No. 40, filed 1/28/03) indicates that the E1 gene of Ad.RSVbgal vector in the prior art reference of Le Gal La Salle *(Science* 259:988-990, February, 1993) had its E1 gene "deleted;" however, discrepancies occur in the Reply to Request for Information in two instances: first, on page 3 this sentence appears: "The adenoviral vectors of Le Gal La Salle differ when comparing the same set of genes because at least the fact that the vectors of Le Gal La Salle possess only a deleted or non-functional E1 gene." In the context of the instant application where Applicant has acted as his own lexicographer, "deleted" and "non-functional" cannot mean the same thing in relation to the E1 gene. Therefore, if Le Gal La Salle teaches a "deleted" E1 gene, it falls short of meeting the "non-functional" E1 gene limitation recited in all of the instant claims. If Le Gal La Salle teaches a "non-functional" E1 gene as defined by Applicant's own specification, Le Gal La Salle meets that critical limitation in all of the instant claims.

Second, the anonymous co-author of the *Science* publication responding to the Reply to

Request for Information states that "More specifically, the Ad.RSVbgal adenovirus is derived from Ad d1327, which is derived from the d1234 specifically noted in Thimmappaya, and thus these two viruses carry the same E3 deletion. The only difference between Ad d1327 and Ad d1324 is that Ad d1327 is not deleted for E1 whereas Ad d1324 is" (underlining added). Because Ad.RSVbgal is derived from Ad d1327 which is not deleted for E1, the Examiner is confused as to how the Ad.RSVbgal vector has an E1 gene deletion.

Specifically, the Examiner requests to know, if possible, clearly and unambiguously without obfuscation, does the Ad.RSVbgal vector reported in Le Gal La Salle *(Science* 259:988-990, February, 1993) have a "deleted" or "non-functional" E1 gene as defined by Applicant's own specification (page 9, line 26 to page 10, line 1)? Additionally, to make the record clear and complete as to who is providing evidence for the record, the identity of the anonymous co-author responding to the Request for Information is requested.

8. For the purposes of the following art rejections, the Examiner is assuming at this time that Le Gal La Salle *(Science* 259:988-990, February, 1993) discloses a RSVbgal vector with a "deleted" E1 gene and not a "non-functional" E1 gene as defined by Applicant's own specification (page 9, line 26 to page 10, line 1).

9. Claims 27-28, 31-35, 37-38, 41, and 48-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barde in view of Wilson et al. (US 5,585,362). Barde discloses an adenovirus encoding human prepro/BDNF cDNA and transfected mammalian cells (column 18, line 32 to column 20, line 53, and column 38, line 7 to column 40, line 18). Barde did not teach

specialized viral promoters for the nervous system or non-functional adenovirus E1 gene. Wilson teaches replication-defective adenovirus (abstract), RSV-LTR promoter, Ad 5 human adenovirus (column 11, lines 54-65), and human cells from lung (column 8, lines 66-67). Wilson does not teach adenovirus comprising prepro/BDNF encoding cDNA. The filing date of Wilson is 6/7/93 and that date is now considered the effective filing date of Wilson in regards as a reference for the instant Application. It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the encoding nucleotide sequences for BDNF and adenovirus vector of Barde and combine that with the replication deficient adenovirus of Wilson because Wilson discloses many advantages for the adenovirus vector for gene therapy, including its approval for clinical trials (column 2, lines 25-26), growth to extremely high titers for production purposes, usefulness in nondividing cells (column 2, lines 58-60) such as neurons (brain cells), and other reasons (column 1, lines 54-62). In addition, replication deficient adenovirus cannot multiply once introduced to the brain, thereby avoiding a potentially uncontrollable viral infection of the brain, as well as avoiding lytic destruction of neurons from replicating virus. The motivation to use the RSV-LTR promoter is to increase the yield of the encoding nucleotides to produce BDNF protein.

Applicant's arguments filed 8/14/01 have been fully considered but they are not persuasive. Applicant has not perfected the foreign filing date sought of 9/25/92, so Wilson is still held as prior art (6/7/93) under 102(e).

Applicant's arguments filed 1/28/03 have been fully considered but they are not

persuasive because Applicant merely asserts that the combination of references represent an obvious to try situation without presenting any evidence to support the assertion. Given that Applicant's methods are substantially the same as the prior art's methods to arrive at the instant invention, Applicant appears to be arguing against the enablement of the instant invention! Applicant also argues the Barde reference in isolation which is not the appropriate standard.

10. Claims 27-28, 31-34, 37, 41, and 48-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barde in view of Levrero et al. ("Levrero"). Barde discloses an adenovirus encoding human prepro/BDNF cDNA and transfected mammalian cells (column 18, line 32 to column 20, line 53, and column 38, line 7 to column 40, line 18). Barde did not teach specialized viral promoters for the nervous system or non-functional adenovirus E1 gene. Levrero teaches replication-defective adenovirus with defective E1 genes (abstract), MLP promoter (abstract), Ad 5 human adenovirus (page 197) and human cells including hepatocytes or liver-derived cells (pages 197-200). Levrero does not teach adenovirus comprising prepro/BDNF encoding cDNA. It would have been obvious to one of ordinary skill in the art at the time the invention was made to make and use the BDNF encoding adenovirus of Barde as a replication defective adenovirus as taught by Levrero in order to treat diseases of the nervous system amenable to BDNF treatment or to produce BDNF protein as suggested by Barde (column 25, line 44 to column 29, line 42) and because replication deficient adenovirus cannot multiply once introduced to the brain, thereby avoiding a potentially uncontrollable viral infection of the brain and avoiding lytic destruction of neurons from replicating virus. In addition, Levrero

teaches that defective adenovirus usually produced higher amounts of protein product than nondefective virus (page 198), providing further motivation as to the choice of defective virus over nondefective. The motivation to use the MLP promoter is to increase the yield of the encoding nucleotides to produce BDNF protein.

Applicant's arguments filed 1/28/03 have been fully considered but they are not persuasive because Applicant merely asserts that the combination of references represent an obvious to try situation without presenting any evidence to support the assertion. Given that Applicant's methods are substantially the same as the prior art's methods to arrive at the instant invention, Applicant appears to be arguing against the enablement of the instant invention!

11. Claims 27-28, 31-33, 37, 41, and 48-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barde in view of Quantin et al. ("Quantin"). Barde discloses an adenovirus encoding human prepro/BDNF cDNA and transfected mammalian cells (column 18, line 32 to column 20, line 53, and column 38, line 7 to column 40, line 18). Barde did not teach specialized viral promoters for the nervous system or non-functional adenovirus E1 gene. Quantin teaches replication-defective adenovirus with defective E1 genes, Ad 5 human adenovirus (pages 2581-2582) and human cells (pages 2581-2582). Quantin does not teach adenovirus comprising prepro/BDNF encoding cDNA. It would have been obvious to one of ordinary skill in the art at the time the invention was made to make and use the BDNF encoding adenovirus of Barde as a replication defective adenovirus as taught by Quantin in order to treat diseases of the nervous system amenable to BDNF treatment or to produce BDNF protein as

suggested by Barde (column 25, line 44 to column 29, line 42) and because replication deficient adenovirus cannot multiply once introduced to the brain, thereby avoiding a potentially uncontrollable viral infection of the brain and avoiding lytic destruction of neurons from replicating virus.

Applicant's arguments filed 1/28/03 have been fully considered but they are not persuasive because Applicant merely asserts that the combination of references represent an obvious to try situation without presenting any evidence to support the assertion. Given that Applicant's methods are substantially the same as the prior art's methods to arrive at the instant invention, Applicant appears to be arguing against the enablement of the instant invention!

12. Claims 27-28, 31-35, 37, 41, and 48-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barde in view of Stratford-Perricaudet et al. ("Stratford-Perricaudet"). Barde discloses an adenovirus encoding human prepro/BDNF cDNA and transfected mammalian cells (column 18, line 32 to column 20, line 53, and column 38, line 7 to column 40, line 18). Barde did not teach specialized viral promoters for the nervous system or non-functional adenovirus E1 gene. Stratford-Perricaudet teaches replication-defective adenovirus with defective E1 genes (page 627), the RSV-LTR promoter (page 626), Ad 5 human adenovirus (page 626) and human cells (pages 626). Stratford-Perricaudet does not teach adenovirus comprising prepro/BDNF encoding cDNA. It would have been obvious to one of ordinary skill in the art at the time the invention was made to make and use the BDNF encoding adenovirus of Barde as a replication defective adenovirus as taught by Stratford-Perricaudet in order to treat diseases of the nervous

system amenable to BDNF treatment or to produce BDNF protein as suggested by Barde (column 25, line 44 to column 29, line 42) and because replication deficient adenovirus cannot multiply once introduced to the brain, thereby avoiding a potentially uncontrollable viral infection of the brain and avoiding lytic destruction of neurons from replicating virus. The motivation to use the RSV-LTR promoter is to increase the yield of the encoding nucleotides to produce BDNF protein.

Applicant's arguments filed 1/28/03 have been fully considered but they are not persuasive because Applicant merely asserts that the combination of references represent an obvious to try situation without presenting any evidence to support the assertion. Given that Applicant's methods are substantially the same as the prior art's methods to arrive at the instant invention, Applicant appears to be arguing against the enablement of the instant invention!

13. No claim is allowed.

14. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however,

will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Gucker whose telephone number is (703) 308-6571. The examiner can normally be reached on Monday to Friday from 0930 to 1800. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623. The fax phone number for this Group is currently (703) 308-4242, but Applicant should confirm this by phoning the Examiner before faxing.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

SG

Stephen Gucker

April 21, 2003

Gary L. Kunz

GARY KUNZ
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